REVIEW

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Optimal Endoscopic Treatment and Surveillance of Serrated Polyps

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Serrated polyps are considered precursor lesions that account for 15% to 30% of colorectal cancers, and they are overrepresented as a cause of interval cancers. They are difficult to detect and resect comprehensively; however, recent data suggest that high definition endoscopy, chromoendoscopy (via spray catheter, pump or orally), narrow band imaging, split-dose bowel preparation and a slower withdrawal (>6 minutes) can all improve detection. Cold snare resection is effective and safe for these lesions, including cold snare piecemeal endoscopic mucosal resection, which is likely to become the standard of care for lesions >10 mm in size. Sessile serrated lesions ≥10 mm in size, those exhbiting dysplasia, or traditional serrated adenomas increase the chance of future advanced neoplasia. Thus, a consensus is emerging: a surveillance examination at 3 years should be recommended if these lesions are detected. Serrated lesions likely carry equivalent risk to adenomas, so future guidelines may consider serrated class lesions and adenomas together for risk stratification. Patients with serrated polyposis syndrome should undergo surveillance every 1 to 2 years once the colon is cleared of larger lesions, and their first degree relatives should undergo screening every 5 years starting at age 40. **(Gut Liver 2020;14:423-429)**

Key Words: Colorectal neoplasms; Serrated polyps; Endoscopic mucosal resection; Endoscopic submucosal dissection; Serrated polyposis syndrome

INTRODUCTION

Colorectal cancer (CRC) is one of the leading causes of mortality around the world. It is the fourth most common cancer worldwide accounting for 6.1% of total cancers diagnosed and second leading cause of cancer related death, after lung cancer, in world.[1] In the United Kingdom, bowel cancer is the 4th most common cancer accounting for 12% of all new cancer diagnosis. Overall, serrated polyps contribute to 20% to 30% of sporadic CRCs.[2] Although serrated lesions are thought to be less common in Asian populations, a number of studies from Korea and Hongkong have suggested similar rates to Western cohorts.[3-5] Failure to detect sessile serrated lesions (SSL) is thought to be one of the reasons for interval CRC[6] and the failure of screening colonoscopy in preventing right sided colon cancers.[7] One of the reasons behind this is that SSL are difficult to detect or visualize during endoscopy due to flat shape and pale or translucent appearance[8] and are often incompletely resected.[9] These issues have implications on what should be the optimal endoscopic treatment and surveillance of serrated polyps which remains area of active research. Through this review, we attempt to address this contentious issue through available literature and evidence.

SESSILE SERRATED POLYPS AND THEIR ENDOSCOPIC DETECTION

Lesion of the serrated class include sessile serrated polyps (SSPs) along with hyperplasic polyps and traditional serrated adenomas form heterogeneous group.[10] SSPs can be further characterized on basis on endoscopic, histological and molecular features. Endoscopic assessment of SSP is challenging. They are often subtle, pale in appearance and are frequently masked by mucous cap.[11] Features suggestive of SSL rather than hyperplastic polyp include dark spots within pits, indistinct boarder, a cloud-like or bosselated surface and irregular shape.[12,13] Dysplastic lesions have transition from flat to nodular, sessile or depressed area; type III–V pit pattern and NICE 2.[14]

They are more common in the right side of colon where less good preparation can make detection challenging. Detection can

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Table 1. Interventions at Colonoscopy That May Improve Serrated Lesion Detection Rates

Beneficial	May be beneficial	No clear benefit
Slower withdrawal >6 min	Endocuff	Antispasmodics
Chromoendoscopy	G-EYE	Good vs adequate bowel
High definition		Preparation
Narrow-band imaging		Wide angle and enhanced mucosal views
Split dose bowel preparation		Right colon retroflexion

Adapted from East JE, et al. Gut 2017;66:1181-1196.[16]

be improved by withdrawing slowly, using high definition colonoscope[15] and chromoendoscopy (dye spray) (Table 1).[16-18] Some early data suggests the use of Endocuff may support SSL (SSA/P) detection with a 15% detection rate with Endocuff versus a 3% rate with standard colonoscopy (p=0.001).[19] A colonoscope with a large balloon at the bending section which slows withdrawal and compresses folds (G-EYE colonoscope; Smart Medical Systems Ltd., Ra'anana, Israel) also improved serrated lesion detection rates in a large randomized controlled study (2.7% vs 0.8%, p=0.036).[20] A study that looked at narrow-band imaging (NBI; Olympus, Tokyo, Japan) for serrated polyp detection suggested a statistical trend toward improved detection with a mean number of serrated lesions proximal to the sigmoid of 0.51 with NBI versus 0.39 for white light (p=0.085).[21] A subsequent meta-analysis of NBI for detection of non-adenomatous (serrated) lesions suggested significantly improved detection with either first or second generation "Bright" NBI.[22] With increasing use of NBI, the Workgroup on Serrated Polyps and Polyposis (WASP)–has described classification (also called WASP) for distinguishing between hyperplastic and adenomatous/serrated polyps (Fig. 1).[23] In WASP classification , criterion like "dark spots inside crypt" are more reliable than criterion "irregular shape." Also, it does not incorporate a commonly used criterion in practice, "mucus cap."

Although higher bowel preparation quality has previously not been shown to be associated with improved serrated lesion detection, a recent meta-analysis suggests that use of split dose bowel preparation does seem to improve serrated lesion detection relative risk of 2.48 (95% confidence interval [CI], 1.21 to 5.09).[24]

ENDOSCOPIC TREATMENT METHODS

The choice of endoscopic resection for any polyp revolves around two principles; safety and recurrence. Recurrence depends heavily on completeness of endoscopic resection. Size more than 10 mm and SSP are two strongest predictors of incomplete endoscopic resection.[9] Hence, removal of SSP of size

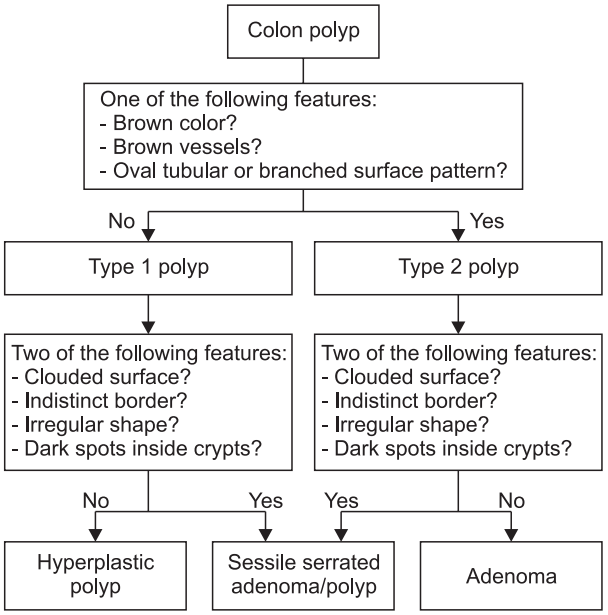

Fig. 1. Workgroup on Serrated Polyps and Polyposis (WASP) classification.

over 10 mm requires expertise. Cold snare polypectomy is the preferred method for removal of SSP less than 10 mm. Relatively little data specific to serrated lesions is available; however in cases series of small polyps which are predominantly adenomatous, cold snaring is a very safe and efficacious method and performs better than cold forceps polypectomy method.[25,26] Rates of complications with cold snare polypectomy are very low and intra procedural bleeding, 1.8% in one large series, is usually controlled with injection or endoscopic clipping.[17] Perforations, which are more of concern with hot snare, are exceptionally rare with cold snare. Majority of the bleed with cold snare are immediate and self-limiting.

Thin wire (0.30 mm) snares have been shown more effective than thick wire (0.47 mm) snares in achieving complete endoscopic and pathologic excision. Horiuchi *et al.*[27] showed, in a prospective randomized controlled trial of 210 polyps, that thin wire snares have significantly more complete pathological resection as compared to thick wire snare (91% vs 79%, p=0.02). In another study Din *et al.*[28] showed there was significantly endoscopic complete resection (90.2% vs 73.3%, p<0.05) and nonsignificant higher trend for complete pathological excision (73.3% vs 65.2%, p=0.4) with thin wire snares. Injection can be helpful to help grasp some normal mucosa around the edges of these flat lesions to maximise chances of comprehensive resection, and adding methylene blue or indigo carmine to the injection fluid and provide contrast to see the edges of the lesion more clearly (Fig. 2).

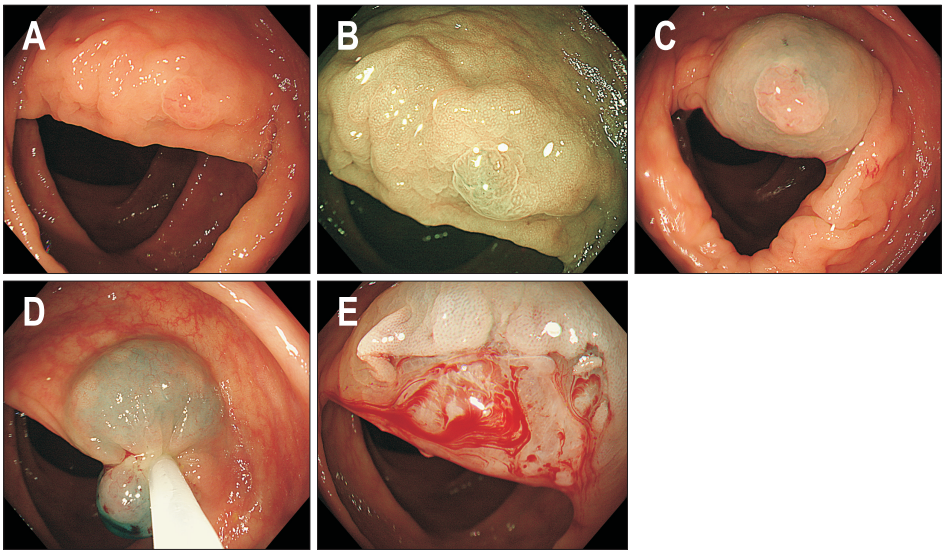

Fig. 2. Cold snare lift and endoscopic mucosal resection of small sessile serrated lesion. (A) A 5-mm serrated polyp observed in the ascending colon. (B) Lesion seen with narrow-band imaging under magnification; note the small black dots within the pits, suggestive of a sessile serrated lesion. (C) Resected lesion with fluid. The specimen was stained with methylene blue as a contrast agent to clarify the lesion edges. (D) Lesion grasped with a thin wire cold snare. Note the additional normal mucosa snared to ensure complete excision. (E) Post-resection defect observed under magnification after washing. Note that normal mucosa can be clearly observed around the edges, confirming excision.

Table 2. Cold Snare Resection of Larger Serrated Lesions

Author (year)	No.	Size, mm	Pathology	Complications	Recurrence, %
Tate *et al*. (2018)[34]	34	10–35	SSP	None	None
Rameshshanker *et al*. (2018)[35]	29	10–30	SSP	None	3.4
Piraka *et al*. (2017)[36]	94	10–60	75 TA/TVA 19 Serrated	Clip ×1	9.7

SSP, sessile serrated polyp; TA, tubular adenomas; TVA, tubulo-villous adenoma.

ENDOSCOPIC MUCOSAL RESECTION OF LARGE SERRATED LESIONS

For lesions greater than 10 mm, endoscopic mucosal resection (EMR) is the preferred technique. It is important to carefully inspect larger lesion as they have more chance to have dysplasia which may appear as subtle change in surface of polyp in form of nodularity, elevation or depression with or without adenomatous pit pattern.[29] EMR is safe and efficacious method of removing larger (>10 mm) SSPs. SSP s are easier to remove by endoscopic resection as compared to adenomas as they do not have submucosal fibrosis and are loosely attached to deeper layers making lifting easy after injection. Rao *et al*.[30] showed, in a large cohort of 251 SSP (>10 mm), EMR could safely remove polyps with only 3.6% recurrence rate after mean follow-up of 17.8±15.4 months. All recurrences (median size, 4 mm) could be managed by endoscopic resection.

In a large cohort of laterally spreading tumors (LST) >20 mm, Pellise *et al*.[31] showed EMR could successfully remove SSP as compared to adenomas with similar adverse events and less bleeding. The same study showed significantly lower rates of recurrence with SSP at 6 months (6.3% vs 16.1%) and 12 months (7.0% vs 20.1%) compared to adenomatous lesions. EMR does have associated complications which involve bleeding (1/10 to 1/30),[32] perforation (1/100) and post polypectomy syndrome (1/200).[33] Given the risks of resection of flat lesion in the right colon, some authors have suggested that the risks of resection may outweigh the cancer prevention benefits; however, we would suggest that cold snare piecemeal EMR (pEMR) is a safe and effective way to resect these larger right sided serrated lesions. Three recent studies have reported cold snare pEMR data, with or without injection to lift the lesion, with acceptable rates of recurrence and low complication rates (Table 2), and it seems likely that cold snare pEMR will become the standard of care for resection of these lesions in the future.[34-36]

ENDOSCOPIC SUBMUCOSAL DISSECTION OF LARGE SERRATED LESIONS

Large SSLs are predominantly right sided, as compared to adenomatous LSTs) which have propensity for being left sided or rectal. The risk of recurrence in large SSLs is lower than equivalent adenomatous lesions, and the risk of invasive cancer is also lower for a lesion of equivalent size.[30] Endoscopic submucosal dissection (ESD) has been described in management of large serrated lesion;[37] however, it has its own technical challenges, e.g., the flap of SSLs is thin and floppy making it difficult to control using standard gravity-based positioning during ESD. Therefore the advantages of use of ESD for which are perhaps clearest for large rectal lesions where the risk of recurrence or invasion

is high, and the consequences of a perforation are lower, are inverted for serrated lesions which are technically difficult to resect, occur in the thin walled right colon, and are low risk for recurrence or invasion.[38-40] We therefore recommend cold snare pEMR for large SSLs, and would only consider ESD for a lesion assessed as high risk for early sub-mucosal invasion. Traditional serrated adenomas are morphologically much more similar to LSTs, are predominantly found in the rectum and may be good targets for ESD. In a large Korean cohort of SSP/adenoma with dysplasia/adenocarcinoma, ESD was used as resection method in 3.8% of patients for SSP ≥20 mm.[41]

SURVEILLANCE

Due to lack of prospective and controlled data, most of the recommendations and guidelines are based on expert opinion and observational data. Table 3 summarizes the current U.S. Multi-Society Task Force (US MSTF),[42] European Society of Gastrointestinal Endoscopy (ESGE)[43] and British Society of Gastroenterology (BSG) position statement guidance on surveillance for serrated polyps (Table 3); however more recently data has become available both on the comparative risk of small and advanced serrated lesions versus adenomas and whether serrated lesions and adenomas should be treated separately or together.

SURVEILLANCE FOR SMALL <10 MM SERRATED LESIONS

The BSG position statement on serrated polyps in the colorectum recommended no surveillance for patients with one or more serrated lesions <10 mm in size who do not meet the criteria for serrated polyposis syndrome (SPS),[16] although US MSTF guidelines suggests 5 yearly surveillance for 1 to 2 serrated lesions <10 mm in size. There are as yet no prospective data to validate this recommendation. Schreiner *et al*.[44] report in a U.S. cohort from more than a decade ago, 248 out of 3,121 patients (7.9%) had at least 1 proximal non-dysplastic serrated polyp (ND-SP). They were more likely than patients with no proximal ND-SP to have advanced neoplasia (17.3% vs 10.0%). During surveillance, 39 patients with baseline proximal ND-SP and no neoplasia were more likely to have neoplasia compared with subjects who did not have polyps (odds ratio [OR], 3.14). Among patients with advanced neoplasia at baseline, those with proximal ND-SP (n=43) were more likely to have advanced neoplasia during surveillance (OR, 2.17). The United States, pathology based case-control study suggested that the rate of CRC was significantly higher in sessile serrated adenomas that in patients with adenomas or hyperplastic polyps over 13 years follow-up (12.5% vs 1.8% vs 1.8%, respectively).[45] All serrated lesions with subsequent cancer were <10 mm in size; however some SPS patients and patients with traditional serrated adenomas were included and it is not clear whether SSAs were resected comprehensively and not just biopsied. In a large Danish case-control cohort, which reanalyzed pathological samples using modern definitions of serrated polyps, serrated lesions alone were broadly risk equivalent to adenomas alone for future cancer risk without considering size.[46] Given that non-advanced serrated lesions appear risk equivalent to non-advanced adenomas, their surveillance should be equivalent, with no surveillance recommended by the BSG position statement or ESGE and that patients should return to population screening.

SURVEILLANCE FOR ADVANCED SERRATED LESIONS (SSL ≥10 MM, SSL WITH DYSPLASIA OR TRADITIONAL SERRATED ADENOMA)

The BSG position statement on serrated polyps in the colorectal recommends one off surveillance colonoscopy at 3 years for patients with an advanced serrated lesion, defined as a SSL ≥10 mm, SSL with dysplasia and traditional serrated adenomas,[16] in line with US MSTF recommendation, and broadly with ESGE recommendation (Table 3). No prospective data to validate this recommendation exists; however, a number of lines of evidence are strongly suggestive that future CRC risk is increased by these lesions to a level consistent with that post advanced adenoma detection. In the Norwegian Colorectal Cancer Prevention (NORCCAP) screening study, large ≥10 mm hyperplastic (serrated) lesions were associated with the same future CRC risk as advanced adenomas, increased 3- to 4-fold versus no polyps.[47] A large Danish cohort which reanalyzed pathological samples using modern definitions of serrated polyps, traditional serrated adenomas and SSL with dysplasia had an almost 5-fold higher risk of future CRC.[46]

Table 3. US MSTF, ESGE and BSG Recommendations for the Surveillance of Sessile Serrated Polyps

Baseline colonoscopy finding	Recommended surveillance interval		
	US MSTF	ESGE	BSG
Size <10 mm without dysplasia	5 yr	10 yr	No surveillance on the basis of serrated polyps
Any lesion ≥10 mm in size or with dysplasia	3 yr	3 yr	One off colonoscopy at 3 yr
Or traditional serrated adenoma	3 yr		One off colonoscopy at 3 yr
Serrated Polyposis syndrome	1 yr	3 yr genetic counselling	1–2 yr once colon cleared consider genetic counselling

US MSTF, U.S. Multi-Society Task Force; ESGE, European Society of Gastrointestinal Endoscopy; BSG, British Society of Gastroenterology.

SERRATED POLYPOSIS SYNDROME SURVEILLANCE

SPS is common in bowel cancer screening programs which use guaiac fecal occult blood testing (gFOBT) or fecal immunochemical testing (FIT) as a screening test, with estimates of SPS prevalence ranging from 1:150 to 1:300.[48,49] A recent Spanish FIT based cohort followed up all their patients with proximal serrated polyps, tripling the number of additional cases of SPS, for a final prevalence of 1:100.[50] Therefore, especially when using FIT in bowel cancer screening, colonoscopists should be alert to a diagnosis of SPS.

US MSTF and ESGE recommend surveillance period of 1 year and 3 years respectively (Table 3).The BSG position statement on serrated polyps in the colorectal recommended 1 to 2 yearly surveillance for patients meeting the World Health Organization (WHO) criteria for SPS.[16] This recommendation was on the basis that in early cohorts, future risk of CRC was elevated at as much as 7% at 5 years;[51,52] however in larger cohorts with rigorous surveillance performed every 1 to 2 years, with all lesions larger than 5 mm in size resected, at academic centers, the risk appeared much lower with CRC only diagnosed at 1.9 cases per 1,000 years of patient follow-up.[53,54] Recent data suggests once the colon is cleared, follow-up can be safely deferred to 2 years.[55,56]

The risk for patient who are first-degree relatives of patients with SPS also appears elevated between 3- to 5-fold compared to the general population[51,57,58] and screening colonoscopy is recommended for this group, with subsequent colonoscopies determined by polyp burden. Surveillance should then be performed every 5 years if no polyps are found.

A recent paper that looked at patients with multiple serrated polyps and adenomas, not quite meeting the criteria for SPS also noted that their risk for CRC was equivalent to patients who met the WHO definition of SPS, and that their first-degree relatives also had an elevated risk of CRC, comparable to the risk for first-degree relatives of SPS patients.[58]

SURVEILLANCE WHEN SERRATED LESIONS AND ADENOMAS ARE FOUND TOGETHER

In previous guidelines it was not possible to comment on how to assign surveillance intervals when serrated lesions occurred together with adenomas and whether risk, and therefore surveillance intervals, should be considered separately for each polyp class or if their risk was additive. At that time, each polyp class was considered separately and the shortest surveillance interval was used.[16] There has been recent data on the future risk when adenomas and serrated lesions are found together. The risk of finding an advanced adenoma at surveillance had an OR for future risk with synchronous advanced adenomas and serrated lesions at index exam 4-fold higher than for advanced adenomas alone. A further similar study from Korea presented in abstract form suggests additive risk between adenomas and SSL with the risk of advanced colorectal neoplasia at 3 years follow-up for adenoma with synchronous serrated polyp being 17.9% versus 10.7% for adenoma alone ($p<0.001$).[59] Audit data from an Australian CRC surveillance program with 2,157 patient followed up for a median of 50 months found additive risk of advanced neoplasia when serrated lesion and adenomas were found together (high-risk adenoma: hazard ratio [HR]=2.04 [95% CI, 1.70 to 2.45]; high-risk SSP+adenoma: HR=3.20 [95% CI 1.31 to 7.82]; low-risk SSP+adenoma: HR=2.20 [95% CI, 1.03 to 4.68]).[60] Older data from the 1990s when serrated lesions were less recognised both endoscopically and pathologically is supportive but less definitive.

CONCLUSION

Adequate resection technique and appropriate surveillance of serrated polyps is of utmost importance as they are a major reason behind interval cancers and failure of screening colonoscopy in preventing right sided colon cancers. Their identification is difficult and challenging but is aided by increased withdrawal time and chromoendoscopy. Cold resection techniques are safe and effective and are increasingly supported by larger cases series data. Surveillance strategies, on the other hand, are currently predominantly based on expert opinion and observational data; however new case series are becoming available to make these recommendations more evidence based.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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